# Crystallization Kinetics of Dispersions of Polyethylene Glycol and Structurally-Related Drugs Containing High Drug Loadings

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**Purpose**

Considering the importance of the crystallization process in determining the properties of the resultant dispersions, and the necessity to get a deeper insight into the crystallization process of semi-crystalline polymers during the formation of dispersions in order to improve the reproducibility and consistency of product qualities, the purpose of this work was to investigate the crystallization behavior of dispersions made up of polyethylene glycol and a series of structurally-related drugs containing high drug loadings.

**Methods**

Dispersions made up of polyethylene glycol 6000 (PEG) and active pharmaceutical ingredient (API) were prepared by heating the mixture of the two components to above the melting temperatures of both components, followed by solidification of the melt.

Thermal properties of dispersions were analyzed using modulated differential scanning calorimetry (m-DSC). The samples were crimped in aluminum DSC pans and subjected to heating from -75°C to above the melting points of mixtures using an underlying heating rate of 5°C/min with a modulating amplitude of 0.636°C and a period of 40 seconds.

For X-ray diffraction analysis, samples were mounted on a (thermostated) sample holder and scanned over a range of $4° \leq 2\theta \leq 40°$ using a step size of 0.0167° and counting time of 200 seconds. Diffractograms were recorded using an automated diffractometer.

The crystallinity of PEG was used as an indicator to monitor the crystallization process of the polymer. The crystallinity data were fitted to the Avrami equation by nonlinear curve fitting.

**Results**

Increasing the drug loading results in higher stability and slows down the crystallization rate of the amorphous polymer which is contradiction to the behavior normally observed with solid dispersions. Drug loading seems to influence the growth geometries of PEG crystals as well as microstructure of dispersions, possibly by changing the interplay between the crystallization rate of the polymer and the diffusion rate of API molecules.

At 52% indomethacin (IMC), PEG was completely transformed to the amorphous state. To the best of our knowledge, this is the first detailed investigation of the solubilization effect of a low molecular weight drug on a semi-crystalline polymer in their dispersions.

In mixtures containing 35% to 55% IMC, the dispersions exhibited distinct glass transition events resulting from amorphous-amorphous phase separation that generates polymer-rich and drug-rich domains upon the solidification of supercooled PEG. In contrast, samples containing below 30% or above 60% IMC showed a single amorphous phase during the period in which crystallization normally occurs.

The same phenomena were also observed for dispersions of PEG and a series of IMC structurally-related drugs such as ketoprofen, suprofen, tiaprofenic acid and flurbiprofen, which points to structure-properties relationship.

**Conclusion**

The current study demonstrates large variation in the physicochemical properties of API/PEG dispersions as a function of drug loading. Giving the complex nature of API/PEG dispersions which is governed by the interplay between numerous factors, these observations are important for preparation of solid dispersions with reproducible and consistent physicochemical properties and pharmaceutical performance.